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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,369	12/26/2006	Philippe Dupraz	ARS.126	2134

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/573,369	DUPRAZ ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-49,51 and 53-56* is/are rejected.

7)☒ Claim(s) *50 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 1/22/10. Claims 45-56 are pending.

Response to Amendments

The following claim amendments were discussed as part of an Examiner's amendment. However, upon further consideration the arguments regarding the rejection under 35 USC 103 has not been deemed persuasive in overcoming this rejection as more specifically set forth below. However, the following amendments are suggested for the following reasons.

To indicate the composition as opposed to a method of forming a construct, the following claim language for claim 45 is recommended.

--Claim 45 (currently amended). A DNA construct comprising a polynucleotide sequence encoding a fusion protein, said fusion protein comprising an immunoglobulin signal peptide (IgSP) fused to a tissue-type plasminogen activator (tPA) propeptide ~~to form an~~ (IgSP-tPA pre-propeptide). --

For clarification and simplification, the following claim language is recommended.

--Claim 48 (previously presented). The DNA construct of claim 45, wherein said tPA propeptide is a human tPA propeptide~~, the carboxyl-terminal extremity of said tPA propeptide consisting of amino acids~~ wherein the carboxy terminus is Arg-Xaa-Arg-Arg.--

As SEQ ID NO:3 is an amino acid, and not a nucleic acid, the following amendment to claims 51 and 53 are recommended.

--Claim 51 (previously presented). The DNA construct of claim 45, wherein said ~~construct~~ IgSP comprises SEQ ID NO: 3 ~~fused to a nucleic acid encoding~~ and said tPA comprises amino acids 23 to 32 of SEQ ID NO: 2.--

--Claim 52 (previously presented). The DNA construct of claim 45, wherein said ~~DNA construct or said construct~~ IgSP comprises SEQ ID NO: 3 ~~fused to~~ and said tPA is encoded by SEQ ID NO: 1.--

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-49, 51 and 53-56 under 35 U.S.C. 103(a) as being unpatentable over Ashkenazi et al (WO9953059; see entire document) in view of Patel et al (WO0052158; see entire document). **This rejection is maintained for reasons of record in the office action mailed 9/25/09 and restated below. The heading has been corrected to include the complete list of claims rejected as listed on the 326.**

Applicants claim a DNA construct comprising SEQ ID NO:3, mouse IgSP operably linked to tPA.

Ashkenazi et al teach a construct comprising a human tissue plasminogen activator signal sequence fused to an IgG 1 sequence (see figure 1 and brief description). The tPA molecule is provided in SEQ ID NO: 1 and 7 of Ashkenazi et al and comprise amino acids 23-32 of SEQ ID

NO:2. Furthermore the sequence can comprise TNFR sequences (a polypeptide of interest). The constructs are grown in CHO cells (¶ 0036) except Ashkenazi et al do not teach that the signal sequence is SEQ I DNO:3.

Patel et al teach construction of a DNA construct encoding a mouse IgSP sequence corresponding to SEQ ID NO:3 operably linked to sequences for export. Patel et al teach that the mouse IgSP is known in the art and predictably can mediate export (see figure 15a).

In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of the recited construct is done applying a known sequence to a known method to improve the construct with predictable results. As well, it is within the ordinary skill of the art to use available methodologies to isolate a variety of signal sequences for use in a heterologous sequence and one would have been motivated to do so in order as the ability to modify sequences by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicants' arguments have been considered but are not persuasive for the following reasons. Applicants argue that neither Ashkenazi et al nor Patel et al are directed to the combination of IgSP and tPA. As an initial point, the Supreme Court particularly emphasized in KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, it is accepted that generation of the recited vector is done applying a know technique to a known method to improve the vector with predictable results. There is no indication in the specification that the particulars of the instant promoter is an advancement over the art that was achieved with unexpected consequences or otherwise unexpected results. As well, it is within the ordinary skill of the art to use available methodologies to isolate a variety of sequences comprising any of a number of promoters and one would have been motivated to do so in order as the ability to modify sequences by applying conventional methodologies. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention. Here, Ashkenazi et al teach a molecule comprising a signal sequence operably linked to a tPA pro-peptide to form a "signal-pro" sequence. The signal sequence can be any signal sequence so long as it performs the function of directing the protein to the lumen of the ER (bolded parts below). The tPA sequence

is designed for secretion of the peptide. Hence, similar to the instant invention, Ashekanzi et al are drawn to a signal-pro sequence to improve secretion and production of the linked protein sequences.

> FIG. 1. Diagram of a tumor necrosis factor immunoglobulin chimeric molecule (TNFR-IgG1) and signal sequences. TNFR-IgG1 is a chimeric protein consisting of the extracellular domain of the p55 TNF receptor fused to the hinge and Fc domain of an immunoglobulin heavy chain. TNFR-IgG1 is secreted as a homodimer with four N-linked glycosylation sites (squares) per monomer. **The proteins expressed in this study were synthesized using the wild type TNFR signal sequence containing 29 amino acids (SEQ ID NO: 2), or a combination of the TNFR signal sequence and the signal and/or pro-sequence of human tissue plasminogen activator (tPA) (SEQ ID NO: 1).**

> "Pre -pro" or "signal -pro" peptide as used in the context of the present invention is meant to refer to an amino acid sequence such as that naturally associated with a mammalian t-PA which acts to direct the secretion of a mature polypeptide, for example, a mammalian t-PA, from a cell. As used herein, the term "signal -pro peptide" includes the "pre-" or "signal" sequence such as that naturally associated with a mammalian t-PA which functions to bind to the signal-recognition particle and direct the protein to the lumen of the endoplasmic reticulum (ER).). **A "signal" sequence is an amino acid sequence, characteristically hydrophobic in nature, cleaved by signal peptidases in the ER. For example, the signal sequence of t-PA is generally removed from the nascent t-PA co-translationally.**
>
> **For example, N- or C-terminal addition of a signal sequence other than that of a mammalian t-PA to mammalian precursor peptide as defined herein is within the scope of the precursor peptide of the invention.**

However, Ashkenazi et al do not teach use of murine IgSP. However, Patel is directed towards use of murine IgSP sequences in recombinant fusion sequences wherein the construct further comprises a secretion sequence. Therefore, Ashkenazi et al and Patel et al are directed to overlapping inventions wherein the format is a leader (signal) sequence-export signal. The specifics of each differ but taken together one would conclude that the signal sequence of Patel et al would function as a heterologous sequence as encompassed by Ashkenazi et al.

> **For example, N- or C-terminal addition of a signal sequence other than that of a mammalian t-PA to mammalian precursor peptide as defined herein is within the scope of the precursor peptide of the invention.**

For the result to be unexpected, it must be commensurate in scope with the claim. See MPEP §716.02(d) which states, " 6.02(d) [R-2] Unexpected Results Commensurate in Scope With Claimed Invention. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." "See also In re Peterson, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); In re Grasselli, 713 F.2d 731,741,218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims.).." In this case, the combined construct represents components found in the art that have been shown to perform functions combined with related elements to enhance protein expression and secretion.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

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